EXHIBIT 12

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Third Edition

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For each degree of urbanization, lung cancer mortality rates in smokers are shown by the dark gray bars, and nonsmoker mortality rates are indicated by light gray bars. From these data we see that in every level (or stratum) of urbanization, lung cancer mortality is higher in smokers than in nonsmokers. Therefore, the observed association of smoking and lung cancer cannot be attributed to level of urbanization. By examining each stratum separately, we, in effect, hold urbanization constant, and still find much higher lung cancer mortality in smokers than in nonsmokers.

For each degree of urbanization, lung cancer mortality rates and smokers are shown by the dark-colored bars, and nonsmoker mortality rates are indicated by light-colored bars. For these data we see that in every level (or stratum) of urbanization, lung cancer mortality is higher in smokers than in nonsmokers. Therefore, the observed association of lung cancer cannot be attributed to level of urbanization. By examining each stratum separately, we are, in effect, holding urbanization constant, and we still find much higher lung cancer mortality in smokers than in nonsmokers.

Multivariate analysis controls for the confounding factor through mathematical modeling. Models are developed to describe the simultaneous effect of exposure and confounding factors on the increase in risk.[135]

Both of these methods allow for adjustment of the effect of confounders. They both modify an observed association to take into account the effect of risk factors that are not the subject of the study and that may distort the association between the exposure being studied and the disease outcomes. If the association between exposure and disease remains after the researcher completes the assessment and adjustment for confounding factors, the researcher must then assess whether an inference of causation is justified. This entails consideration of the Hill factors explained in Section V, *infra*.

V. General Causation: Is an Exposure a Cause of the Disease?

Once an association has been found between exposure to an agent and development of a disease, researchers consider whether the association reflects a true cause–effect relationship. When epidemiologists evaluate whether a cause–effect relationship exists between an agent and disease, they are using the term causation in a way similar to, but not identical to, the way that the familiar "but for," or sine qua non, test is used in law for cause in fact. "Conduct is a factual cause of

135. For a more complete discussion of multivariate analysis, see Daniel L. Rubinfeld, Reference Guide on Multiple Regression, in this manual.

[harm] when the harm would not have occurred absent the conduct."[136] This is equivalent to describing the conduct as a necessary link in a chain of events that results in the particular event.[137] Epidemiologists use causation to mean that an increase in the incidence of disease among the exposed subjects would not have occurred had they not been exposed to the agent.[138] Thus, exposure is a necessary condition for the increase in the incidence of disease among those exposed.[139] The relationship between the epidemiologic concept of cause and the legal question of whether exposure to an agent caused an individual's disease is addressed in Section VII.

As mentioned in Section I, epidemiology cannot prove causation; rather, causation is a judgment for epidemiologists and others interpreting the epidemiologic data.[140] Moreover, scientific determinations of causation are inherently tentative. The scientific enterprise must always remain open to reassessing the validity of past judgments as new evidence develops.

In assessing causation, researchers first look for alternative explanations for the association, such as bias or confounding factors, which are discussed in Section IV, *supra*. Once this process is completed, researchers consider how guidelines for inferring causation from an association apply to the available evidence. We emphasize that these guidelines are employed only *after* a study finds an association

136. Restatement (Third) of Torts: Liability for Physical and Emotional Harm § 26 (2010); *see also* Dan B. Dobbs, The Law of Torts § 168, at 409–11 (2000). When multiple causes are each operating and capable of causing an event, the but-for, or necessary-condition, concept for causation is problematic. This is the familiar "two-fires" scenario in which two independent fires simultaneously burn down a house and is sometimes referred to as overdetermined outcomes. Neither fire is a but-for, or necessary condition, for the destruction of the house, because either fire would have destroyed the house. *See* Restatement (Third) of Torts: Liability for Physical and Emotional Harm § 28 (2010). This two-fires situation is analogous to an individual being exposed to two agents, each of which is capable of causing the disease contracted by the individual. *See* Basko v. Sterling Drug, Inc., 416 F.2d 417 (2d Cir. 1969). A difference between the disease scenario and the fire scenario is that, in the former, one will have no more than a probabilistic assessment of whether each of the exposures would have caused the disease in the individual.

137. *See supra* note 7; *see also* Restatement (Third) of Torts: Liability for Physical and Emotional Harm § 26 cmt. c (2010) (employing a "causal set" model to explain multiple elements, each of which is required for an outcome).

138. "The imputed causal association is at the group level, and does not indicate the cause of disease in individual subjects." Bruce G. Charlton, *Attribution of Causation in Epidemiology: Chain or Mosaic?* 49 J. Clin. Epidemiology 105, 105 (1999).

139. *See* Rothman et al., *supra* note 61, at 8 ("We can define a cause of a specific disease event as an antecedent event, condition, or characteristic that was necessary for the occurrence of the disease at the moment it occurred, given that other conditions are fixed."); Allen v. United States, 588 F. Supp. 247, 405 (D. Utah 1984) (quoting a physician on the meaning of the statement that radiation causes cancer), *rev'd on other grounds,* 816 F.2d 1417 (10th Cir. 1987).

140. Restatement (Third) of Torts: Liability for Physical and Emotional Harm § 28 cmt. c (2010) ("[A]n evaluation of data and scientific evidence to determine whether an inference of causation is appropriate requires judgment and interpretation.").

to determine whether that association reflects a true causal relationship.[141] These guidelines consist of several key inquiries that assist researchers in making a judgment about causation.[142] Generally, researchers are conservative when it comes to assessing causal relationships, often calling for stronger evidence and more research before a conclusion of causation is drawn.[143]

The factors that guide epidemiologists in making judgments about causation (and there is no threshold number that must exist) are[144]

141. In a number of cases, experts attempted to use these guidelines to support the existence of causation in the absence of any epidemiologic studies finding an association. *See, e.g.,* Rains v. PPG Indus., Inc., 361 F. Supp. 2d 829, 836–37 (S.D. Ill. 2004) (explaining Hill criteria and proceeding to apply them even though there was no epidemiologic study that found an association); Soldo v. Sandoz Pharms. Corp., 244 F. Supp. 2d 434, 460–61 (W.D. Pa. 2003). There may be some logic to that effort, but it does not reflect accepted epidemiologic methodology. *See In re* Fosamax Prods. Liab. Litig., 645 F. Supp. 2d 164, 187–88 (S.D.N.Y. 2009); Dunn v. Sandoz Pharms. Corp., 275 F. Supp. 2d 672, 678–79 (M.D.N.C. 2003) ("The greater weight of authority supports Sandoz' assertion that [use of] the Bradford Hill criteria is a method for determining whether the results of an epidemiologic study can be said to demonstrate causation and not a method for testing an unproven hypothesis."); *Soldo*, 244 F. Supp. 2d at 514 (the Hill criteria "were developed as a mean[s] of interpreting an established association based on a body of epidemiologic research for the purpose of trying to judge whether the observed association reflects a causal relation between an exposure and disease." (quoting report of court-appointed expert)).

142. *See* Mervyn Susser, Causal Thinking in the Health Sciences: Concepts and Strategies in Epidemiology (1973); Gannon v. United States, 571 F. Supp. 2d 615, 624 (E.D. Pa. 2007) (quoting expert who testified that the Hill criteria are "'well-recognized' and widely used in the science community to assess general causation"); Chapin v. A & L Parts, Inc., 732 N.W.2d 578, 584 (Mich. Ct. App. 2007) (expert testified that Hill criteria are the most well-utilized method for determining if an association is causal).

143. Berry v. CSX Transp., Inc., 709 So. 2d 552, 568 n.12 (Fla. Dist. Ct. App. 1998) ("Almost all genres of research articles in the medical and behavioral sciences conclude their discussion with qualifying statements such as 'there is still much to be learned.' This is not, as might be assumed, an expression of ignorance, but rather an expression that all scientific fields are open-ended and can progress from their present state. . . ."); Hall v. Baxter Healthcare Corp., 947 F. Supp. 1387 app. B. at 1446–51 (D. Or. 1996) (report of Merwyn R. Greenlick, court-appointed epidemiologist). In *Cadarian v. Merrell Dow Pharmaceuticals, Inc.,* 745 F. Supp. 409 (E.D. Mich. 1989), the court refused to permit an expert to rely on a study that the authors had concluded should not be used to support an inference of causation in the absence of independent confirmatory studies. The court did not address the question whether the degree of certainty used by epidemiologists before making a conclusion of cause was consistent with the legal standard. *See* DeLuca v. Merrell Dow Pharms., Inc., 911 F.2d 941, 957 (3d Cir. 1990) (standard of proof for scientific community is not necessarily appropriate standard for expert opinion in civil litigation); Wells v. Ortho Pharm. Corp., 788 F.2d 741, 745 (11th Cir. 1986).

144. *See* Cook v. Rockwell Int'l Corp., 580 F. Supp. 2d 1071, 1098 (D. Colo. 2006) ("Defendants cite no authority, scientific or legal, that compliance with all, or even one, of these factors is required. . . . The scientific consensus is, in fact, to the contrary. It identifies Defendants' list of factors as some of the nine factors or lenses that guide epidemiologists in making judgments about causation. . . . These factors are not tests for determining the reliability of any study or the causal inferences drawn from it.").

1. Temporal relationship,
2. Strength of the association,
3. Dose–response relationship,
4. Replication of the findings,
5. Biological plausibility (coherence with existing knowledge),
6. Consideration of alternative explanations,
7. Cessation of exposure,
8. Specificity of the association, and
9. Consistency with other knowledge.

There is no formula or algorithm that can be used to assess whether a causal inference is appropriate based on these guidelines.[145] One or more factors may be absent even when a true causal relationship exists.[146] Similarly, the existence of some factors does not ensure that a causal relationship exists. Drawing causal inferences after finding an association and considering these factors requires judgment and searching analysis, based on biology, of why a factor or factors may be absent despite a causal relationship, and vice versa. Although the drawing of causal inferences is informed by scientific expertise, it is not a determination that is made by using an objective or algorithmic methodology.

These guidelines reflect criteria proposed by the U.S. Surgeon General in 1964[147] in assessing the relationship between smoking and lung cancer and expanded upon by Sir Austin Bradford Hill in 1965[148] and are often referred to as the Hill criteria or Hill factors.

145. *See* Douglas L. Weed, *Epidemiologic Evidence and Causal Inference,* 14 Hematology/Oncology Clinics N. Am. 797 (2000).

146. *See* Cook v. Rockwell Int'l Corp., 580 F. Supp. 2d 1071, 1098 (D. Colo. 2006) (rejecting argument that plaintiff failed to provide sufficient evidence of causation based on failing to meet four of the Hill factors).

147. Public Health Serv., U.S. Dep't of Health, Educ., & Welfare, Smoking and Health: Report of the Advisory Committee to the Surgeon General (1964); *see also* Centers for Disease Control and Prevention, U.S. Dep't of Health & Human Servs., The Health Consequences of Smoking: A Report of the Surgeon General (2004).

148. *See* Austin Bradford Hill, *The Environment and Disease: Association or Causation?* 58 Proc. Royal Soc'y Med. 295 (1965) (Hill acknowledged that his factors could only serve to assist in the inferential process: "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*."). For discussion of these criteria and their respective strengths in informing a causal inference, see Gordis, *supra* note 32, at 236–39; David E. Lilienfeld & Paul D. Stolley, Foundations of Epidemiology 263–66 (3d ed. 1994); Weed, *supra* note 144.

A. Is There a Temporal Relationship?

A temporal, or chronological, relationship must exist for causation to exist. If an exposure causes disease, the exposure must occur before the disease develops.[149] If the exposure occurs after the disease develops, it cannot have caused the disease. Although temporal relationship is often listed as one of many factors in assessing whether an inference of causation is justified, this aspect of a temporal relationship is a necessary factor: Without exposure before the disease, causation cannot exist.[150]

With regard to specific causation, a subject dealt with in detail in Section VII, *infra*, there may be circumstances in which a temporal relationship supports the existence of a causal relationship. If the latency period between exposure and outcome is known,[151] then exposure consistent with that information may lend credence to a causal relationship. This is particularly true when the latency period is short and competing causes are known and can be ruled out. Thus, if an individual suffers an acute respiratory response shortly after exposure to a suspected agent and other causes of that respiratory problem are known and can be ruled out, the temporal relationship involved supports the conclusion that a causal relationship exists.[152] Similarly, exposure outside a known latency period constitutes evidence, perhaps conclusive evidence, against the existence of causation.[153] On the other hand, when latency periods are lengthy, variable, or not known and a

149. *See* Carroll v. Litton Sys., Inc., No. B-C-88-253, 1990 U.S. Dist. LEXIS 16833, at *29 (W.D.N.C. 1990) ("[I]t is essential for . . . [the plaintiffs' medical experts opining on causation] to know that exposure preceded plaintiffs' alleged symptoms in order for the exposure to be considered as a possible cause of those symptoms. . . .").

150. Exposure during the disease initiation process may cause the disease to be more severe than it otherwise would have been without the additional dose.

151. When the latency period is known—or is known to be limited to a specific range of time—as is the case with the adverse effects of some vaccines, the time frame from exposure to manifestation of disease can be critical to determining causation.

152. For courts that have relied on temporal relationships of the sort described, see Bonner v. ISP Technologies, Inc., 259 F.3d 924, 930–31 (8th Cir. 2001) (giving more credence to the expert's opinion on causation for acute response based on temporal relationship than for chronic disease that plaintiff also developed); Heller v. Shaw Industries, Inc. 167 F.3d 146 (3d Cir. 1999); Westberry v. Gislaved Gummi AB, 178 F.3d 257 (4th Cir. 1999); Zuchowicz v. United States, 140 F.3d 381 (2d Cir. 1998); Creanga v. Jardal, 886 A.2d 633, 641 (N.J. 2005); Alder v. Bayer Corp., AGFA Div., 61 P.3d 1068, 1090 (Utah 2002) ("If a bicyclist falls and breaks his arm, causation is assumed without argument because of the temporal relationship between the accident and the injury [and, the court might have added, the absence of any plausible competing causes that might instead be responsible for the broken arm].").

153. *See In re* Phenylpropanolamine (PPA) Prods. Liab. Litig., 289 F. Supp. 2d 1230, 1238 (W.D. Wash. 2003) (determining expert testimony on causation for plaintiffs whose exposure was beyond known latency period was inadmissible).

substantial proportion of the disease is due to unknown causes, temporal relationship provides little beyond satisfying the requirement that cause precede effect.[154]

B. How Strong Is the Association Between the Exposure and Disease?[155]

The relative risk is one of the cornerstones for causal inferences.[156] Relative risk measures the strength of the association. The higher the relative risk, the greater the likelihood that the relationship is causal.[157] For cigarette smoking, for example, the estimated relative risk for lung cancer is very high, about 10.[158] That is, the risk of lung cancer in smokers is approximately 10 times the risk in nonsmokers.

A relative risk of 10, as seen with smoking and lung cancer, is so high that it is extremely difficult to imagine any bias or confounding factor that might account for it. The higher the relative risk, the stronger the association and the lower the chance that the effect is spurious. Although lower relative risks can reflect causality, the epidemiologist will scrutinize such associations more closely because there is a greater chance that they are the result of uncontrolled confounding or biases.

154. These distinctions provide a framework for distinguishing between cases that are largely dismissive of temporal relationships as supporting causation and others that find it of significant persuasiveness. *Compare* cases cited in note 151, *supra*, *with* Moore v. Ashland Chem. Inc., 151 F.3d 269, 278 (5th Cir. 1998) (giving little weight to temporal relationship in a case in which there were several plausible competing causes that may have been responsible for the plaintiff's disease), *and* Glastetter v. Novartis Pharms. Corp., 252 F.3d 986, 990 (8th Cir. 2001) (giving little weight to temporal relationship in case studies involving drug and stroke).

155. Assuming that an association is determined to be causal, the strength of the association plays an important role legally in determining the specific causation question—whether the agent caused an individual plaintiff's injury. *See infra* Section VII.

156. *See supra* Section III.A.

157. *See* Miller v. Pfizer, Inc., 196 F. Supp. 2d 1062, 1079 (D. Kan. 2002) (citing this reference guide); Landrigan v. Celotex Corp., 605 A.2d 1079, 1085 (N.J. 1992). The use of the strength of the association as a factor does not reflect a belief that weaker effects occur less frequently than stronger effects. *See* Green, *supra* note 47, at 652–53 n.39. Indeed, the apparent strength of a given agent is dependent on the prevalence of the other necessary elements that must occur with the agent to produce the disease, rather than on some inherent characteristic of the agent itself. *See* Rothman et al., *supra* note 61, at 9–11.

158. *See* Doll & Hill, *supra* note 6. The relative risk of lung cancer from smoking is a function of intensity and duration of dose (and perhaps other factors). *See* Karen Leffondré et al., *Modeling Smoking History: A Comparison of Different Approaches,* 156 Am. J. Epidemiology 813 (2002). The relative risk provided in the text is based on a specified magnitude of cigarette exposure.

C. Is There a Dose–Response Relationship?

A dose–response relationship means that the greater the exposure, the greater the risk of disease. Generally, higher exposures should increase the incidence (or severity) of disease.[159] However, some causal agents do not exhibit a dose–response relationship when, for example, there is a threshold phenomenon (i.e., an exposure may not cause disease until the exposure exceeds a certain dose).[160] Thus, a dose–response relationship is strong, but not essential, evidence that the relationship between an agent and disease is causal.[161]

159. *See* Newman v. Motorola, Inc., 218 F. Supp. 2d 769, 778 (D. Md. 2002) (recognizing importance of dose–response relationship in assessing causation).

160. The question whether there is a no-effect threshold dose is a controversial one in a variety of toxic substances areas. *See, e.g.,* Irving J. Selikoff, Disability Compensation for Asbestos-Associated Disease in the United States: Report to the U.S. Department of Labor 181–220 (1981); Paul Kotin, *Dose–Response Relationships and Threshold Concepts,* 271 Ann. N.Y. Acad. Sci. 22 (1976); K. Robock, *Based on Available Data, Can We Project an Acceptable Standard for Industrial Use of Asbestos? Absolutely,* 330 Ann. N.Y. Acad. Sci. 205 (1979); Ferebee v. Chevron Chem. Co., 736 F.2d 1529, 1536 (D.C. Cir. 1984) (dose–response relationship for low doses is "one of the most sharply contested questions currently being debated in the medical community"); *In re* TMI Litig. Consol. Proc., 927 F. Supp. 834, 844–45 (M.D. Pa. 1996) (discussing low-dose extrapolation and no-dose effects for radiation exposure).

Moreover, good evidence to support or refute the threshold-dose hypothesis is exceedingly unlikely because of the inability of epidemiology or animal toxicology to ascertain very small effects. *Cf.* Arnold L. Brown, *The Meaning of Risk Assessment,* 37 Oncology 302, 303 (1980). Even the shape of the dose–response curve—whether linear or curvilinear, and if the latter, the shape of the curve—is a matter of hypothesis and speculation. *See* Allen v. United States, 588 F. Supp. 247, 419–24 (D. Utah 1984), *rev'd on other grounds,* 816 F.2d 1417 (10th Cir. 1987); *In re* Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig., 524 F. Supp. 2d 1166, 1180 (N.D. Cal. 2007) (criticizing expert for "primitive" extrapolation of risk based on assumption of linear relationship of risk to dose); Troyen A. Brennan & Robert F. Carter, *Legal and Scientific Probability of Causation for Cancer and Other Environmental Disease in Individuals,* 10 J. Health Pol'y & L. 33, 43–44 (1985).

The idea that the "dose makes the poison" is a central tenet of toxicology and attributed to Paracelsus, in the sixteenth century. *See* Bernard D. Goldstein & Mary Sue Henifin, Reference Guide on Toxicology, Section I.A, in this manual. It does not mean that any agent is capable of causing any disease if an individual is exposed to a sufficient dose. Agents tend to have specific effects, *see infra* Section V.H., and this dictum reflects only the idea that there is a safe dose below which an agent does not cause any toxic effect. *See* Michael A Gallo, *History and Scope of Toxicology,* in Casarett and Doull's Toxicology: The Basic Science of Poisons 1, 4–5 (Curtis D. Klaassen ed., 7th ed. 2008). For a case in which a party made such a mistaken interpretation of Paracelsus, see Alder v. Bayer Corp., AGFA Div., 61 P.3d 1068, 1088 (Utah 2002). Paracelsus was also responsible for the initial articulation of the specificity tenet. *See infra* Section V.H.

161. Evidence of a dose–response relationship as bearing on whether an inference of general causation is justified is analytically distinct from determining whether evidence of the dose to which a plaintiff was exposed is required in order to establish specific causation. On the latter matter, see *infra* Section VII; Restatement (Third) of Torts: Liability for Physical and Emotional Harm § 28 cmt. c(2) & rptrs. note (2010).

D. Have the Results Been Replicated?

Rarely, if ever, does a single study persuasively demonstrate a cause–effect relationship.[162] It is important that a study be replicated in different populations and by different investigators before a causal relationship is accepted by epidemiologists and other scientists.[163]

The need to replicate research findings permeates most fields of science. In epidemiology, research findings often are replicated in different populations.[164] Consistency in these findings is an important factor in making a judgment about causation. Different studies that examine the same exposure–disease relationship generally should yield similar results. Although inconsistent results do not necessarily rule out a causal nexus, any inconsistencies signal a need to explore whether different results can be reconciled with causality.

E. Is the Association Biologically Plausible (Consistent with Existing Knowledge)?[165]

Biological plausibility is not an easy criterion to use and depends upon existing knowledge about the mechanisms by which the disease develops. When biological plausibility exists, it lends credence to an inference of causality. For example, the conclusion that high cholesterol is a cause of coronary heart disease is plausible because cholesterol is found in atherosclerotic plaques. However, observations have been made in epidemiologic studies that were not biologically plausible at the time but subsequently were shown to be correct.[166] When an observation is inconsistent with current biological knowledge, it should not be discarded, but

162. In *Kehm v. Procter & Gamble Co.*, 580 F. Supp. 890, 901 (N.D. Iowa 1982), *aff'd*, 724 F.2d 613 (8th Cir. 1983), the court remarked on the persuasive power of multiple independent studies, each of which reached the same finding of an association between toxic shock syndrome and tampon use.

163. This may not be the legal standard, however. *Cf.* Smith v. Wyeth-Ayerst Labs. Co., 278 F. Supp. 2d 684, 710 n.55 (W.D.N.C. 2003) (observing that replication is difficult to establish when there is only one study that has been performed at the time of trial).

164. *See* Cadarian v. Merrell Dow Pharms., Inc., 745 F. Supp. 409, 412 (E.D. Mich. 1989) (holding a study on Bendectin insufficient to support an expert's opinion, because "the study's authors themselves concluded that the results could not be interpreted without independent confirmatory evidence").

165. A number of courts have adverted to this criterion in the course of their discussions of causation in toxic substances cases. *E.g., In re* Phenylpropanolamine (PPA) Prods. Liab. Litig., 289 F. Supp. 2d 1230, 1247–48 (W.D. Wash. 2003); Cook v. United States, 545 F. Supp. 306, 314–15 (N.D. Cal. 1982) (discussing biological implausibility of a two-peak increase of disease when plotted against time); Landrigan v. Celotex Corp., 605 A.2d 1079, 1085–86 (N.J. 1992) (discussing the existence vel non of biological plausibility); *see also* Bernard D. Goldstein & Mary Sue Henifin, Reference Guide on Toxicology, Section III.E, in this manual.

166. *See In re* Rezulin Prods. Liab. Litig., 369 F. Supp. 2d 398, 405 (S.D.N.Y. 2005); *In re* Phenylpropanolamine (PPA) Prods. Liab. Litig., 289 F. Supp. 2d 1230, 1247 (W.D. Wash. 2003).

the observation should be confirmed before significance is attached to it. The saliency of this factor varies depending on the extent of scientific knowledge about the cellular and subcellular mechanisms through which the disease process works. The mechanisms of some diseases are understood quite well based on the available evidence, including from toxicologic research, whereas other mechanism explanations are merely hypothesized—although hypotheses are sometimes accepted under this factor.[167]

F. Have Alternative Explanations Been Considered?

The importance of considering the possibility of bias and confounding and ruling out the possibilities is discussed above.[168]

G. What Is the Effect of Ceasing Exposure?

If an agent is a cause of a disease, then one would expect that cessation of exposure to that agent ordinarily would reduce the risk of the disease. This has been the case, for example, with cigarette smoking and lung cancer. In many situations, however, relevant data are simply not available regarding the possible effects of ending the exposure. But when such data are available and eliminating exposure reduces the incidence of disease, this factor strongly supports a causal relationship.

H. Does the Association Exhibit Specificity?

An association exhibits specificity if the exposure is associated only with a single disease or type of disease.[169] The vast majority of agents do not cause a wide vari-

167. *See* Douglas L. Weed & Stephen D. Hursting, *Biologic Plausibility in Causal Inference: Current Methods and Practice,* 147 Am. J. Epidemiology 415 (1998) (examining use of this criterion in contemporary epidemiologic research and distinguishing between alternative explanations of what constitutes biological plausibility, ranging from mere hypotheses to "sufficient evidence to show how the factor influences a known disease mechanism").

168. *See supra* Sections IV.B–C.

169. This criterion reflects the fact that although an agent causes one disease, it does not necessarily cause other diseases. *See, e.g.,* Nelson v. Am. Sterilizer Co., 566 N.W.2d 671, 676–77 (Mich. Ct. App. 1997) (affirming dismissal of plaintiff's claims that chemical exposure caused her liver disorder, but recognizing that evidence supported claims for neuropathy and other illnesses); Sanderson v. Int'l Flavors & Fragrances, Inc., 950 F. Supp. 981, 996–98 (C.D. Cal. 1996); *see also* Taylor v. Airco, Inc., 494 F. Supp. 2d 21, 27 (D. Mass. 2007) (holding that plaintiff's expert could testify to causal relationship between vinyl chloride and one type of liver cancer for which there was only modest support given strong causal evidence for vinyl chloride and another type of liver cancer).

When a party claims that evidence of a causal relationship between an agent and one disease is relevant to whether the agent caused another disease, courts have required the party to show that

ety of effects. For example, asbestos causes mesothelioma and lung cancer and may cause one or two other cancers, but there is no evidence that it causes any other types of cancers. Thus, a study that finds that an agent is associated with many different diseases should be examined skeptically. Nevertheless, there may be causal relationships in which this guideline is not satisfied. Cigarette manufacturers have long claimed that because cigarettes have been linked to lung cancer, emphysema, bladder cancer, heart disease, pancreatic cancer, and other conditions, there is no specificity and the relationships are not causal. There is, however, at least one good reason why inferences about the health consequences of tobacco do not require specificity: Because tobacco and cigarette smoke are not in fact single agents but consist of numerous harmful agents, smoking represents exposure to multiple agents, with multiple possible effects. Thus, whereas evidence of specificity may strengthen the case for causation, lack of specificity does not necessarily undermine it where there is a good biological explanation for its absence.

I. Are the Findings Consistent with Other Relevant Knowledge?

In addressing the causal relationship of lung cancer to cigarette smoking, researchers examined trends over time for lung cancer and for cigarette sales in the United States. A marked increase in lung cancer death rates in men was observed, which appeared to follow the increase in sales of cigarettes. Had the increase in lung cancer deaths followed a decrease in cigarette sales, it might have given researchers pause. It would not have precluded a causal inference, but the inconsistency of the trends in cigarette sales and lung cancer mortality would have had to be explained.

VI. What Methods Exist for Combining the Results of Multiple Studies?

Not infrequently, the scientific record may include a number of epidemiologic studies whose findings differ. These may be studies in which one shows an association and the other does not, or studies that report associations, but of different

the mechanisms involved in development of the disease are similar. Thus, in *Austin v. Kerr-McGee Refining Corp.*, 25 S.W.3d 280 (Tex. App. 2000), the plaintiff suffered from a specific form of chronic leukemia. Studies demonstrated a causal relationship between benzene and all leukemias, but there was a paucity of evidence on the relationship between benzene and the specific form of leukemia from which plaintiff suffered. The court required that plaintiff's expert demonstrate the similarity of the biological mechanism among leukemias as a condition for the admissibility of his causation testimony, a requirement the court concluded had not been satisfied. *Accord In re* Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig., 524 F. Supp. 2d 1166, 1183 (N.D. Cal. 2007); Magistrini v. One Hour Martinizing Dry Cleaning, 180 F. Supp. 2d 584, 603 (D.N.J. 2002).